

REMARKS

Applicants respectfully requests entry of the amendments and remarks submitted herein. Claims 50, 51, and 60 have been amended.

At page 2 of the Final Office Action the Examiner noted that the amendment dated 9-27-07 is acknowledged and that claims 1-71 are pending. This latter statement is inaccurate. In light of the amendments filed 9-27-07, claims 1-23, 30, 40-42, and 47-71 are pending.

Acknowledgement of this fact is requested.

Claims 50, 51, and 60 were rejected under 35 USC § 112 as being indefinite for containing a term that lacked antecedent basis. Claims 50, 51, and 60 have been amended to recite an anthracycline chemotherapeutic agent. This amendment is believed to obviate the Examiner's ground for rejection. Accordingly, withdrawal of the rejection is requested.

Applicant thanks the Examiner for pointing out these inconsistencies.

Claims 1-44, 47-48, 51 and 58-71 were rejected under 35 USC § 103(a) as being unpatentable over EP 0 719 546 and WO 99/13816 in combination. This rejection is respectfully traversed. It is noted that the Examiner withdrew the previous rejection over EP 0 719 546 and WO 99/13816 by themselves.

Independent claims 1, 63, and 71 recite the following:

- (a) contacting liposomes in an aqueous solution of up to about 60 mM of an acid with an anthracycline chemotherapeutic agent, at a temperature wherein the protonated form of the anthracycline chemotherapeutic agent is charged and is not capable of permeating the membrane of the liposomes, and wherein the unprotonated form of the anthracycline chemotherapeutic agent is uncharged and is capable of permeating the membrane of the liposomes;
- (b) actively loading the liposomes with the anthracycline chemotherapeutic agent by raising the pH of the solution to 5.0 or above;
- (c) cooling the solution to a temperature at which the unprotonated form of the anthracycline chemotherapeutic agent is not capable of permeating the membrane of the liposomes; and
- (d) contacting the solution with a weak base that is an ammonium salt or an alkyl amine, in an amount effective to

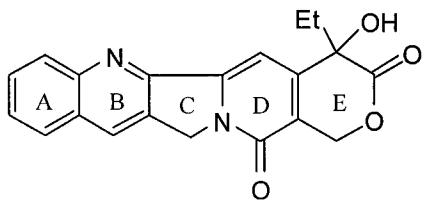
raise the pH of the internal liposome to provide gradient loaded liposomes

WO 99/13816 discusses methods for loading liposomes with camptothecins.

EP 0 719 546 discusses gradient loading of liposomes – however, EP 0 719 546 does not disclose a process that includes steps c and d above. Additionally, EP does not discuss loading any camptothecin compounds.

In order to make a rejection under 35 U.S.C. 103(a) the Examiner first must establish a *prima facie* case of obviousness. Three criteria must be met: 1) there must be some suggestion or motivation, either in the reference or in the knowledge generally available to one of ordinary skill in the art, to modify the reference; 2) there must be a reasonable expectation of success; and 3) the prior art reference must teach all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not be based on applicants disclosure. M.P.E.P. 2142.

The Examiner has not provided any explanation regarding why one skilled in the art would have had a reasonable expectation that the disclosure of WO 99/13816 could have been combined with the disclosure of EP 0 719 546 as suggested by the Examiner. The camptothecins discussed in WO 99/13816 comprise the following ring system, wherein the lactone ring E can be open or closed (please see WO 99/13816 at pages 8-10):



These camptothecin compounds differ significantly in chemical structure from the agents that were loaded in EP 0 719 546. The camptothecin compounds also have significantly different physical properties (e.g. molecular weights, melting points, lipophilicities, solubilities, etc.) from the anthracycline chemotherapeutic agents recited in the instant claims. Because the camptothecins discussed in WO 99/13816 differ significantly from the compounds discussed in EP 0 719 546, it is respectfully submitted that one skilled in the art would not have had a reasonable expectation that that compounds discussed in EP 0 719 546 would be operative in the

loading methods discussed WO 99/13816. This is especially true, since the loading process discussed in EP 0 719 546 does not include steps c and d recited in the claims. Accordingly, the Examiner has not established that the instant claims are *prima facie* obvious over WO 99/13816 in combination with EP 0 719 546. Withdrawal of the rejection is appropriate and is requested.

Additionally, it is submitted that the Examiner has not provided any evidence to support his conclusion that one of ordinary skill in the art would be motivated to load any active agent in WO 99/13816, since EP 0 719 546, which uses a similar loading procedure, teaches that several active agents including anthracycline compounds could be loaded using a pH method (Office action at page 4 lines 7-10). As discussed above, there are significant differences between the agents discussed in the two cited documents. Accordingly, Applicant submits that the Examiner is taking "official notice" that one of ordinary skill in the art would be motivated to load any active agent in WO 99/13816. If the Office maintains the rejection over WO 99/13816 in combination with EP 0 719 546, under 37 C.F.R. 1.104(d)(2), the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support this finding. Thus, if the Office maintains the rejection, in the next communication Applicant respectfully requests that the Examiner provide an affidavit or declaration setting forth specific factual statements and explanation to support the conclusion that one of ordinary skill in the art would be motivated to load any active agent in WO 99/13816.

At page 4 of the Office action, the Examiner states "it is the Examiner's position that the method of loading of an ionic compound would be the same and it would be obvious to one skilled in the art to load any ionic compound with reasonable expectation of success." The Examiner has not provided any evidence to support this conclusion. As discussed above, there are significant differences between the agents discussed in the two cited documents.

Accordingly, Applicant submits that the Examiner is taking "official notice" that method of loading of an ionic compound would be the same and it would be obvious to one skilled in the art to load any ionic compound with reasonable expectation of success. If the Office maintains the rejection over WO 99/13816 in combination with EP 0 719 546, under 37 C.F.R. 1.104(d)(2), the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support this finding. Thus, if the Office maintains the rejection, in the next communication Applicant respectfully requests that the Examiner provide an affidavit or

declaration setting forth specific factual statements and explanation to support the conclusion that one of ordinary skill in the art would be motivated to load any active agent in WO 99/13816.

Additionally, at page 5 of the Office action, the Examiner cites *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007) to support the rejection. It is respectfully submitted that the holding of the Court in KSR does not support the current rejection. KSR involved the positioning of an electronic sensor on an adjustable accelerator pedal for an automobile. Accordingly, the relevant invention in KSR was mechanical in nature (*i.e.* an electronic sensor/pedal combination). The KSR Court based its holding on the idea that “the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” Thus predictability was a significant factor in the KSR holding. It is respectfully submitted that the electrical sensor in KSR represented a predictable mechanical device. One skilled in the art would have had no reason to assume that such a sensor would have operated in an unpredictable manner depending on the sensor’s location on an accelerator pedal.

In contrast, the instant invention relates to the comparatively unpredictable fields of chemistry and pharmacology. Due to the structural and physical variability (e.g. molecular weights, melting points, lipophylicities, solubilities, etc.) between different compounds, they do not always represent simple interchangeable elements. Thus, the reasonable level of predictability for chemical compounds in a complex environment is completely different than the reasonable level of predictability for the electric sensors in KSR. Because the relevant facts in KSR differ dramatically from the relevant facts in the instant application, it is respectfully submitted that the holding of the Court in KSR does not support the current rejection.

The Examiner has also rejected claims 7, 45-46 and 49 under 35 USC § 103(a) as being as being unpatentable over EP 0 719 546, WO 99/13816 in combination, further in view of Webb (5,814,335) of record.

At page 5 of the office action the Examiner stated that what is lacking in EP 0 719 546 and WO 99/13816 is the use of sphingomyelin as a liposome forming lipid. As discussed above, the independent claims 1, 63, and 71 are not obvious over EP 0 719 546 and WO 99/13816, in combination. It is respectfully submitted that the secondary document Webb does not cure the deficiencies discussed above, since it was only cited with respect to sphingomyelin as a liposome forming lipid. Accordingly, the instant claims are not obvious over the disclosures of EP 0 719

546 and WO 99/13816, in combination, further in view of Webb (5,814,335). Withdrawal of this rejection is respectfully requested.

The Examiner has also rejected claims 52-57 under 35 USC § 103(a) as being unpatentable over EP 0 719 546, WO 99/13816 in combination, further in view of Clerc (5,939,096).

At page 6 of the office action the Examiner stated that what is lacking in EP 0 719 546 and WO 99/13816 is the teaching of dehydrating the liposomes in the presence of cryoprotectants. As discussed above, the independent claims 1, 63, and 71 are not obvious over EP 0 719 546 and WO 99/13816, in combination. It is respectfully submitted that the secondary document Clerc does not cure the deficiencies discussed above, since it was only cited with respect to dehydrating the liposomes in the presence of cryoprotectants. Accordingly, the instant claims are not obvious over the disclosures of EP 0 719 546 and WO 99/13816, in combination, further in view of Clerc (5,939,096). Withdrawal of this rejection is respectfully requested.

The Examiner has provisionally rejected claims 1-71 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-42 and 47-71 of copending Application No. 10/723,431. Since this is a provisional rejection, Applicant will wait until otherwise patentable subject matter is identified in both cases before determining if a terminal disclaimer is appropriate. Applicant thanks the Examiner for identifying this potentially relevant issue.

The Examiner has also rejected claims 1-71 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 30-31 and 35-64 of U.S. Patent No. 6,740,335 in combination with EP 0 719 546 cited above.

US Patent 6,740,335 is related to WO 99/13816. In the instant office action, the Examiner rejected the pending claims under 35 USC 103(a) as obvious over EP 0 719 546 and WO 99/13816, in combination. It is respectfully submitted that the instant claims are non-obvious over the claims of US 6,740,335 in combination with EP 0 719 546 for the reasons presented above in response to the 35 USC 103(a) rejection over EP 0 719 546 and WO 99/13816, in combination. Accordingly, withdrawal of the obviousness type double patenting rejection over claims 30-31 and 35-64 of US Patent 6,740,335 in combination with EP 0 719 546 is appropriate and is requested.

Applicant : Ning Hu et al.
Serial No. : 10/723,610
Filed : November 26, 2003
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Attorney's Docket No.: 01992.006US1

CONCLUSION

The Examiner is invited to contact Applicant's Representative at the below-listed telephone number if there are any questions regarding this Response or if prosecution of this application may be assisted thereby.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 50-3503. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account 50-3503.

Respectfully submitted,

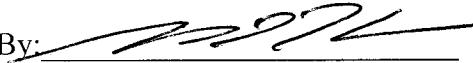
Ning Hu et al.

By their Representatives,

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